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December 4, 2000

Docket Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Proposed Rule, Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use, Docket No. 00N-1463

Dear Sir:

Abbott Laboratories is pleased to have the opportunity to provide comments on the Proposed Rule on Antibiotic Drug Labeling as published on September 19, 2000 in the Federal Register. We propose the attached comments and suggestions to help strengthen the utility of the proposed labeling rule.

On behalf of the 57,000 Abbott employees who help produce healthcare products marketed in more than 130 countries we thank you for your consideration of our comments.

Sincerely,

D. L. Sporn

Douglas L. Sporn
Divisional Vice-President
Corporate Regulatory Affairs

Cc: Jeanne Fox, Abbott Laboratories

00N-1463

C16

Comments to the Proposed Rule "Proposed Labeling Requirements for Systemic Antibacterial Products"

GENERAL COMMENTS

We applaud the FDA for taking steps to try to curtail inappropriate use of antibacterials in an attempt to slow and/or change the development of antibacterial resistance by bacteria. We wish to make the following comments regarding the description of the Proposed Rule:

Inappropriate use should be defined. Inappropriate use includes use of an antibacterial for an infection where the effect of the antibacterial is expected to be no better than placebo, such as use of antibacterials for common respiratory viral infections.

Of note, recently the FDA has determined that secondary bacterial infection of acute bronchitis is no longer to be granted as an indication for routine use of antibacterials. This decision was based on review of a number of placebo-controlled trials. However, a number of drugs still have this indication and are actively promoted for this use. This lack of indication should be uniformly applied to all antibacterials, including those agents that still have this indication in their labeling.

The following are also examples of inappropriate use of antibacterials that have not been addressed in the Description of the Proposed Rule.

Inappropriate use of antibacterials also includes use of a broad-spectrum antibacterial for treatment of an infection when a more appropriate agent of narrower spectrum is available. This point is addressed the supplementary information, section B. "Responding to the Resistance Problem" as a part of the reminders to the physician or health care provider. However, the description of the proposed rule does not include the specific wording that would be used or indicate where this information is to be presented in the labeling.

Inappropriate use may also be defined as using a less potent agent when a more potent agent (with appropriate spectrum) would be more appropriate. This concept of potency is based on in vitro microbiological, pharmacokinetic and pharmacodynamic data. A more potent agent may have a higher concentration of drug at the site of the infection, or a lower MIC or larger AUC/MIC or Time Above MIC relative to a less potent agent of the same class. The more potent agent would be less likely to encourage emergence of resistant bacteria.

Inappropriate use may also be defined as using an antibacterial with an excessively long half-life (which results in long periods of sub-therapeutic tissue or plasma concentrations). In this situation, an antibacterial with a similar spectrum and shorter half-life would be more appropriate. The presence of an antibacterial at sub-therapeutic concentrations is a known mechanism for selecting resistant strains in the microbiology laboratory.

The Proposed Rule puts an inordinate amount of credence in MIC data obtained from *in vitro* testing. These data are unproven as predictors of clinical outcome in many diseases and are unlikely to be relevant to treatment of community acquired respiratory infections, particularly in the outpatient setting.

Additional factors have not been included that are relevant to minimizing emergence of resistant bacteria and that are critical to the clinical outcome of the patient. These factors include pharmacodynamic data, including tissue concentrations or drug concentrations at the site of infection. They also include host factors, including risk factors for drug-resistant bacterial infections.

We agree that in an ideal world, culture and susceptibility testing would be reliable, rapid, and easily obtained. Thus, treatment could be rapidly tailored to the specific bacterial pathogen. However, in the current era, none of these points are true.

The majority of infections are treated empirically, primarily because delay in initiating treatment is unethical and impractical. For the majority of infections, including respiratory tract infections, obtaining a specimen for culture that provides evidence for a definitive pathogen in not possible; most pathogens are considered presumptive, based on culture of material from non-sterile sites.

Outpatient treatment of presumptive bacterial infections is empiric, and no cultures are obtained for the vast majority. The current medical environment is not conducive to use of microbiological diagnostic procedures. Because of CLIA regulations, Gram stains may not be performed and interpreted by clinical health care professionals; qualified laboratory technicians must perform them. Because of consolidation and other efforts to decrease the cost of medical care, few clinics have ready access to local microbiology laboratories. Further, the constraints of managed health care negatively impact the use of these facilities. Many of our nation's hospitals also do not currently have their own microbiology laboratories. The majority of microbiological diagnostic testing is performed in central locations by a relatively few laboratories, which require transport to the site prior to culture, and who are not readily accessible to the clinicians. The IDSA has recently written a Position Paper that addresses the lack of microbiology laboratory access and training, and the threat that this lack of facilities poses to our national health care. However, unless the current situation changes, drug product labeling is unlikely to impact the frequency of collection of culture and susceptibility information.

Susceptibility data obtained from surveillance studies have limitations for prospective therapeutic decisions. These data are important for monitoring the change in the rates of resistance, but their limitations need to be recognized. Large national and international surveillance studies generally obtain their isolates from hospitalized patients. These patients are inherently at greater risk for harboring isolates classified as resistant, and data obtained from these surveys are biased. These large studies are usually performed using standardized methods recommended by the NCCLS. These data are

unlikely to be linked to clinical data, such that the clinical relevance of the MIC values generated is limited.

Local surveillance data contain additional opportunities for bias. Sample sizes are smaller and less likely to represent the larger population of the local community. The methods used by the microbiology laboratory may not follow the NCCLS recommendations.

Laboratory methodology and expertise can influence the outcome of susceptibility testing. An example is the use of E-strips for testing for susceptibility. These are frequently in error for drugs that are highly dependent on pH for activity, and can result in large variations. This is a particularly significant issue with macrolides, such as erythromycin and clarithromycin. An example of this problem is demonstrated in the Trust studies. Based on isolates collected during the 1996-97 respiratory season using the E-test testing method and NCCLS breakpoints, which are based on microbroth dilution, the rate of *H. influenzae* susceptible to clarithromycin was reported to be 58% (n=1572, Diagn Microbiol Infect Dis 1997:29:249-257). A second publication, by the same authors and based on isolates obtained in that same season, which utilized the microbroth dilution method, reported the rate of *H. influenzae* susceptible to clarithromycin as 92% (n=1032, AAC 43:2612-2623).

Surveillance data is rare in the outpatient setting, as the standard of care is empiric therapy. Data from hospitalized patients cannot be used to predict the susceptibility data of outpatients. What data is available has primarily been generated from clinical trials sponsored by pharmaceutical companies, and are generally comprised of isolates from patients who are not at risk for having resistant organisms. This lack of risk is because of the entry criteria determined based on FDA guidance's for conduct of clinical trials exclude patients who would be at risk for resistant isolates (i.e., recent antibacterial therapy or hospitalization, residence in a chronic care facility, immunocompromised host status, significant uncontrolled co-morbid diseases).

The molecular resistance mechanisms for particular bacteria may be useful in some situations to predict clinical efficacy. There is evidence that *in vitro* susceptibility profiles for *S. pneumoniae* that contain resistance genes for penicillin binding proteins or β-lactamase positive *H. influenzae* are relevant for treatment of meningitis. *N. gonorrhoeae* diseases, and many nosocomial infections, particularly *S. aureus* and *Pseudomonas aeruginosa*, and some of the Gram negative enteric pathogens, have also been demonstrated to have *in vitro* susceptibility profiles that are predictive of clinical outcome of therapy, particularly if genes coding for resistance mechanisms have been incorporated into the bacterium. The presence of a mutation in the ribosomal RNA for mycobacteria species or *H. pylori* is significant for predicting response to macrolide therapy. However, the presence of this mutation in *S. pneumoniae* is unlikely to be relevant for predicting response to therapy in respiratory infections, as *S. pneumoniae* has multiple copies of the gene. In addition, *S. pneumoniae* has two additional resistance mechanisms for macrolides, efflux (mef A) and ribosomal methylase (erm AM). The clinical significance of these resistance mechanisms is still under evaluation; however,

few isolates have been identified from patients with specific diseases treated with macrolides.

The location of the infection predicts the response to therapy in some specific diseases, but not all diseases. For example, meningitis, which is considered a closed space infection, is much more dependent on the susceptibility of the invading bacterium to the specific antibacterial. This is the only disease caused by *S. pneumoniae* for which experts currently recommend treatment based on the assumption that the organism is resistant to penicillin (Sanford Guide to Antimicrobial Therapy, 2000).

Guidelines for treatment of respiratory tract infections currently do not use surveillance data to guide most empiric therapy. The CDC-drug-resistant *S. pneumoniae* therapeutic working group for acute otitis media recommends that "oral amoxicillin should remain the first line antimicrobial agent for treating acute otitis media (AOM)" (Ped Infect Dis J 1999. 18:1-9). The recommendations for empiric treatment of community acquired pneumonia issued by the CDC-drug-resistant *S. pneumoniae* therapeutic working group (Arch Intern Med 2000. 160:1399-1408), the Canadian Thoracic Society (Clin Infect Dis 2000. 31:383-421), and the Infectious Diseases Society of America (Clin Infect Dis 2000. 31:347-382) recommend first line, empiric therapy without consideration of surveillance data. All three guidelines continue to recommend macrolides as first line, they differ with regard to how they position doxycycline and the respiratory quinolones. They also address the importance of drug-resistant bacteria and the patient populations at risk for resistant bacterial pathogen. These guidelines undergo frequent updates to include the most recent evidence-based information.

Clinical outcome data are NOT the basis for current NCCLS and FDA breakpoints for most drugs used for outpatient respiratory tract infections. The majority of *in vitro* susceptibility breakpoints for drugs used to treat respiratory tract infections, as established by the NCCLS, have been based on population frequency distributions. These frequency distributions are determined early in the life of the particular drug, and usually at a time when little or no *in vitro* resistance is present in these populations. This is particularly relevant for the macrolide class. Following is an excerpt from the NCCLS meeting minutes regarding macrolide breakpoints.

From Attachment II of the Minutes of the Fastidious Organisms Working Group :Summary Minutes Subcommittee on Antimicrobial Susceptibility testing Boston Massachusetts June 5-7,1994.

"Dr. Jorgensen noted that the breakpoints for non-fastidious organisms did not fit well with the scatter grams for azithromycin and clarithromycin. Therefore, alternative MIC breakpoints and zone sizes for testing *S. pneumoniae* were proposed by Dr. Jorgensen and accepted by the working group for Table 2C in M7-A3 and M2-A% as follows:"

	S	I	R
Azi.	< 0.5	1.0	> 2
	< 18	17-14	> 13mm
clari.	< 0.5	1.0	> 2
	< 21	20-17	> 16mm

From the:Summary Minutes Subcommittee on Antimicrobial Susceptibility testing Chicago Illinois June 11-13., 1995. Attachment III Working group on fastidious Microorganisms. The full subcommittee approved the breakpoints for streptococci and pneumococci for erythromycin, clarithromycin and azithromycin in an effort to match the population distributions, provide approximately equal resistance distributions for all agents, and to harmonize the breakpoints between the two groups of streptococci. Frequency distributions of pneumococcal data from Dr. Doern and MIC distributions for Group A streptococci from Dr. Mary York confirmed that these breakpoints were reasonable for the two organisms.

	S	I	R
Erythromycin	< 0.25	0.5	> 1
Clarithromycin	< 0.25	0.5	> 1
Azithromycin	< 0.5	1	> 2

These breakpoints for macrolides do not include pharmacodynamic data, particularly regarding concentrations at the site of infection, and do not include information regarding clinical outcome. Our own clinical trial data, while of limited amount, indicates that for AECB and CAP, the MIC for either *S. pneumoniae* or *H. influenzae* has no relationship to clinical outcome.

The NCCLS has made recent changes to the breakpoints for some, but not all, β-lactam antibacterials. These changes in breakpoints have altered the susceptibility rates for many of these agents, based primarily on pharmacodynamic data (but not on clinical data). For example, amoxicillin now has a breakpoint for resistance of 8 μg/mL, while the previous breakpoint was 2 μg/mL. (reference to Table 2G. MIC Interpretive Standards for *S. pneumoniae*. NCCLS Performance standards for antimicrobial susceptibility testing. 10th Informational Supplement. NCCLS Document M100-S10 (M7) Jan 2000. NCCLS 940 West Valley Road, Suite 1400, Wayne PA 19087-1898 USA)

These changes in the breakpoints influence the results of resistance rates for surveillance data, such *that S. pneumoniae* went from a national rate of high-level resistance of 16% to 4%. Meanwhile, penicillin breakpoints were not changed, although both drugs initially had similar MIC values for resistant organisms. Thus, the high-level resistance rate remains at 16% for penicillin. These values are misleading and confusing to the practicing physician. This "unlevel playing field" is likely to continue for some time, as it will take a number of review cycles for the NCCLS to evaluate new pharmacodynamic data and review current antibacterial breakpoints.

Recommending the use of local epidemiology and susceptibility patterns will drive use of newer, possibly broader-spectrum, agents that have lower rates of *in vitro* resistance when older agents, including generic agents, are still appropriate choices. This recommendation suggests that susceptibility data do predict clinical outcome, and would lead to use of these data in promotional activities. This is inconsistent with the requirements of DDMAC regarding disclaimer statements, such as "the clinical significance of these data are unknown" that are currently required when using *in vitro* data in promotional materials.

Clinicians should determine whether antibacterial therapy should be changed based on clinical situation, not merely on *in vitro* susceptibility data. The standard of clinical practice regarding use of susceptibility data is based on the clinical outcome or course of the patient. If the patient is doing well on the current therapy it will be continued. If the patient is not improving, the clinician may choose to change or add therapy based on the susceptibility profile of the presumed pathogen.

Only recently has it been possible in clinical trials to assess the impact of *in vitro* resistance; the FDA guidelines were revised in 1997, so that patients with bacterial isolates that had *in vitro* MIC values considered to be resistant no longer were required to be discontinued from therapy. The investigator determines if the patient requires a change in therapy, based on clinical presentation. Adding a statement to the label indicating that *in vitro* susceptibility testing should lead to a change in empiric therapy would negate this recent change. It would also make it impossible to obtain data to show the clinical response of patients with presumptive bacterial infections considered to be resistant. Our own clinical experiences during 1997-2000 indicate that for treatment of acute bacterial exacerbation of chronic bronchitis and community acquired pneumonia in the outpatient setting, the *in vitro* susceptibility data do not correlate with clinical outcome.

The following are recommended changes to the Proposed Rule:

1. Proposed changes to Proposed Sec. 201.24 (a). "Inappropriate use of antibacterial agents, including (insert name of antibacterial drug product), may increase the prevalence of drug resistant ~~microorganisms~~ bacteria and may decrease the effectiveness of antibacterial agents, including the (insert name of antibacterial drug product) ~~and related antimicrobial agents~~. ~~Use~~ (insert name of antibacterial drug product) should be used only to treat infections that are proven or ~~strongly~~ suspected to be cause by ~~susceptible microorganisms~~ indicated bacteria. ~~See Indications and Usage section.~~"

   Because this particular proposed rule applies to antibacterials and drug resistant bacteria, wording should be limited to these drugs and organisms (i.e., antibiotics or antibacterial agents; not antimicrobials or antimicrobial agents).

   'Strongly' does not add to the term "suspected", therefore, we recommend deleting this word.

   The term 'antibacterial agents' has been added, because there is cross-resistance among drugs of a particular class. In addition, the term 'related antimicrobial agents' has been deleted. Many resistant bacteria are multi-drug resistant, and these resistance genes reside on a plasmid, which may be passed to a previously susceptible bacterium, rendering it resistant to several classes in one step.

'Indicated' should be used to describe bacteria. The indications and usage section of the label describes indicated bacteria. A number of reasons to not emphasize 'susceptible' are given above.

2. Proposed changes to Proposed Sec. 201.24 (b). "Appropriate use of antibacterial agents ~~the drug product~~ includes, where applicable, identification of the causative ~~microorganism~~ bacteria and determination of its susceptibility profile." "The pharmacokinetic and pharmacodynamic profile of the agent and the location of the infection should also be considered when selecting an appropriate antibiotic for treatment of a documented or presumptive infection."

   The second sentence is added to emphasize additional clinical pharmacology data relevant to the selection of appropriate antibiotic therapy.

3. Proposed changes to Proposed Sec. 201.24 (c).

   Delete this statement. For a number of reasons noted above, this statement is not applicable for all antibacterials or for many indications. It has the potential to result in actions that are contrary to the intent of the "Proposed Rule".

4. Proposed changes to Proposed Sec. 201.24 (d). "Inappropriate use of antibacterial agents, including (insert name of antibacterial drug product), may increase the prevalence of drug resistant ~~microorganisms~~ bacteria, and may decrease the future effectiveness of ~~(insert name of antibacterial drug product) and related antimicrobial agents~~ antibacterial agents, including the drug product. ~~(Insert name of antibacterial drug product)~~ Antibacterial agents, including the drug product, should ~~only~~ be used to treat infections that are proven or ~~strongly~~ suspected to be caused by indicated bacteria~~. See Indications and Usage section~~." The antibacterial agent chosen to treat a documented or presumptive bacterial infection should be targeted to the most likely bacterial pathogen(s) and should have the narrowest spectrum possible to cover the likely pathogen(s).

   Reasons for the proposed changes are listed under Comment 1. (above). In addition, the additional sentence would address the need for targeted therapy, as mentioned in Section B. of the Supplementary Information: Background.

5. Proposed Sec. 201.24 (e) " 'Information for Patients'
   - Patients should be counseled that antibacterial drugs, including (insert name of antibacterial drug product), should only be used to treat bacterial infections. ~~It does~~ These antibiotics do not treat viral infections (e.g., the common cold)."
   - Patients should also be told that the medication should be taken exactly as directed. Skipping doses and not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria ~~will~~ may develop that ~~will~~ may not be treatable by ~~(insert name of antibacterial drug product)~~ antibacterial drugs in the future.

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